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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,438	BROWNING ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11,12,17,18 and 22-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,11,12,17,18 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/02; ~~6/18/04~~*. 7/12/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 17 December 2004 has been entered in full. Claims 1, 4-7, 11-12 are amended. Claims 2-3, 8-10, 13-16, and 19-21 are cancelled. Claims 22-28 are added.

Election/Restrictions

Applicant's election with traverse of Group II, claims 1-15, 17-18 (and new claims 22-28), drawn to a method of inhibiting B cell growth in an animal comprising administering an anti-BAFF antibody in the reply filed on 17 December 2004 is acknowledged. The traversal is on the ground(s) that the Examiner did not explicitly state that all methods recited in the preambles of clams 1-15 and 17-18 in the definition of Group II directed to include: a method of inhibiting B cell growth (claims 1 and 8-15), a method of inhibiting immunoglobulin production (claims 2 and 8-15), a methods of inhibiting dendritic cell-induced B cell growth and maturation (claims 3 and 8-15), a methods of treating an autoimmune disease (claims 4 and 8-15), a method of treating hypertension (claims 5 and 8-15), a method of treating renal disorders (claims 6 and 8-15), a method of treating B-cell lymphoproliferative disorders (claims 7 and 8-15), and a method of inhibiting inflammation (claims 17-18). This is not found persuasive. Specifically, Applicant's arguments as to why Inventions I-IV should be rejoined is not clear to the Examiner. In the restriction of 06 October 2004, Examiner acknowledges that although she did not recite each and every claim preamble in the explanation of the different groups, the independent claims in Groups I-II all recited the same method step. The Examiner properly stated the reasons why Inventions I-IV are distinct. For example, Inventions I-III are unrelated methods. Invention I is

directed to a method of administering a therapeutically effective amount of *a composition consisting of a BAFF-R polypeptide of a chimeric molecule comprising a BAFF-R polypeptide or fragment thereof*, which is not required by the other methods. Invention II is directed to a method of administering a therapeutically effective amount of *a composition consisting of an anti-BAFF-R antibody homolog*, which is not required by the other methods. Invention III is directed to a method of administering an effective amount of an agent, which is not required by the other methods. Inventions IV and I are related as product and process of use. In the instant case, the BAFF-R pharmaceutical composition of Group IV can be used in materially different methods, such as to generate antibodies or in diagnostic assays. Finally, Inventions II/III and IV are unrelated because the product of Group IV is not used or otherwise involved in the processes of Group II and III.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 4-7, 11-12, 17-18, and 22-28 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement filed 12 July 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. It is noted that the journal article references were not received by the Office and therefore, not considered by the Examiner.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in Figure 3 are not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Drawings

2. The drawings are objected to because Figure 1 has a box containing the terms "Figure 2A-2B" in the bottom left corner. Additionally, Figure 7 is dark and the Examiner is unable to interpret the results. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

3. The disclosure is objected to because of the following informalities:

3a. At pg 5 of the specification, the Brief Description of the Figures does not refer to Figures 2A-2B.

3b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHODS OF TREATMENT BY ADMINISTERING AN ANTI-BAFF ANTIBODY".

Appropriate correction is required.

Claim Objections

4. Claims 1, 4-7, 17-18, and 28 are objected to because of the following informalities:

4a. Claims 1, 4-7, 17-18 use the acronym "BAFF-R" without first defining what it represents in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

4b. Claim 28, line 1 is missing a word after the term "antibody".

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 4-7, 11, 17-18, and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 7, and 11 of copending Application No. 10/115,192. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of administering to a mammal a therapeutically effective amount of a composition comprising an anti-BAFF-R (anti-APRIL-R) antibody. The claims recite a different acronym (BAFF-R and APRIL-R) for the same polypeptide. It is noted that the BAFF-R of SEQ ID NO: 1 of the instant application is 100% identical to the APRIL-R of SEQ ID NO: 8 of Application No. 10/115,192. Therefore, the claims of the instant application are not patentably distinct over the copending claims in Application No. 10/115,192.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-7, 11-12, 17-18, are 22-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of inhibiting B-cell growth, or immunoglobulin production, or both comprising the step of administering a therapeutically effective amount of an anti-BAFF-R antibody. The claims recite a method of treatment of an autoimmune disease, a method of treating hypertension, a method of treating renal disorders, a method of treating B-cell lympho-proliferate disorders, and a method of inhibiting inflammation comprising the step of administering an anti-BAFF-R antibody. The claims recite that the anti-BAFF-R antibody binds to a BAFF-R polypeptide. The claims recite that the anti-BAFF-R antibody is monoclonal, recombinantly produced, humanized, and chimeric.

(i) The specification of the instant application teaches that "both monoclonal and polyclonal antibodies (Ab) directed against BAFF-R, and their co-receptors, and antibody fragments such as Fab' and $F(ab')_2$, can be used to block the action of the BAFF-R and its respective co-receptors" (pg 14, lines 6-8). The specification also discloses that antagonistic antibodies would be defined by the lack of agonistic activity and the ability to inhibit receptor-ligand interactions (pg 22, lines 26-29). However, the specification of the instant application does not teach any methods or workings examples that indicate an anti-BAFF-R antibody inhibits B-cell growth or immunoglobulin production or treats an autoimmune disease, hypertension, renal disorders, B-cell lympho-proliferate disorders, and inflammation. Undue experimentation would be required of the skilled artisan to determine the optimal, quantity, duration, and possible route of administration of the anti-BAFF-R antibody. There is little or no guidance in the specification indicating what tissues or organs are being specifically targeted by the anti-BAFF-R antibody.

Administration of the antibody (particularly systemic) would be unpredictable because the skilled artisan would not be able to determine the effect the antibody would have throughout the body. For instance, would the anti-BAFF-R antibody inhibit the proliferation, differentiation, and survival of all lymphocytes, especially B cells, in the body? There is little or no guidance in the specification disclosing the administration of an anti-BAFF-R antibody. This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, the present invention is unpredictable and complex wherein one skilled in the art may not necessarily inhibit B cell growth or immunoglobulin production or treat any autoimmune disease, renal disorder, B-cell lympho-proliferate disorder, hypertension, or inflammation by administration of an anti-BAFF-R antibody. Although the claimed method utilizes routine techniques, the results of the method are unpredictable and complex when combined with the step of administering an anti-BAFF-R antibody.

(ii) Furthermore, the instant specification and claims disclose that an anti-BAFF-R antibody can be administered to treat a myriad of autoimmune diseases, renal disorders, and B-cell lympho-proliferate disorders, among other diseases. However, the numerous autoimmune diseases, renal disorders, and B-cell lympho-proliferate disorders encompassed by claims have different pathophysiologies. For example, regarding just autoimmune diseases, rheumatoid arthritis is a chronic, systemic inflammatory disease that is characterized by synovial inflammation and structural damage of articular cartilage and subchondral bone (pg 325-326;

Elgert, K. Immunology, understanding the immune system. New York: Wiley-Liss, Inc., 1996). Graves' disease is a disorder of the thyroid gland that is caused by autoantibodies that stimulate thyroid cellular activity by displacing thyroid-stimulating hormone binding (Elgert, K., pg 324, col 2). Asthma is characterized by a constriction of the bronchioles of the lung wherein the tissue surrounding the capillaries of the lung contains mast cells, which, when stimulated by allergen, release histamine, causing contraction of the smooth muscles (Elgert, K., pg 305, col 2). Undue experimentation would be required of the skilled artisan to administer an anti-BAFF-R antibody to individuals with all possible autoimmune disorders and diseases and treat the disorder or disease. One skilled in the art would also not be able to predict from the instant specification that an anti-BAFF-R antibody would be able to treat all possible autoimmune disorders (such as rheumatoid arthritis and Graves' disease), renal disorders, and B-cell lympho-proliferate disorders, which have different pathophysiologies. Increased B cell activity is not the only characteristic of autoimmune diseases, renal disorders, and B-cell lympho-proliferate disorders and BAFF-R is not the only stimulant of B cells, particularly B cells directed to produce antibodies to self antigens as in autoimmune diseases.

(iii) Additionally, at the time the invention was made, the state of the art was such that problems were often encountered in the effort to use antibodies, particularly monoclonal antibodies, as clinical reagents. A few of these problems included: the human immune response to foreign antibodies, low affinity or nonoptimal systemic half-life of antibodies, and difficulty in producing sufficient quantities of antibody for therapy (Moore, Clin. Chem 35: 1849-1853, 1989). Additionally, Ballow et al. (J Am Med Assoc 278(22): 2008-2017, 1997) report that humanized monoclonal antibodies, although less antigenic than chimeric monoclonal antibodies,

still elicit antibody production against the idiotypic determinants on the hypervariable region portion of the Ig molecule, shortening serum half-lives (pg 2010, col 3). Ballow et al. also indicate that administration of a chimeric anti-TNF-α monoclonal antibody caused a significant improvement and reduction in acute-phase reactants in patients with rheumatoid arthritis (pg 2011, col 2-3). However, 4-8 weeks after treatment, most patients had disease relapse and retreatment only resulted in temporary improvement (pg 2011, col 3). Ballow et al. state that to achieve continued suppression of the inflammatory response, prolonged or repeated treatment of anti-TNF-α monoclonal antibodies would be necessary (pg 2011, first full ¶). Ballow et al. also conclude that the safety of long-term anti-cytokine therapy remains unknown (pg 2011, first full ¶).

(iv) The specification of the instant application does not teach all possible anti-BAFF-R antibodies. Undue experimentation would be required of the skilled artisan to generate all possible anti-BAFF-R antibodies. There is also little guidance in the specification and the claims as to the structural limitations of the anti-BAFF-R antibody and/or what specific amino acid sequence it binds to.

(v) The specification of the instant application teaches that " 'BAFF-R variant' means an active BAFF-R as defined below having at least about 80% amino acid sequence identity with the BAFF-R having the deduced amino acid sequence shown in SEQ ID NO: 1 for a full-length native sequence BAFF-R or with a BAFF-R ECD sequence. Such BAFF-R variants include, for instance, BAFF-R polypeptides wherein one or more amino acid residues are added, or deleted, at the end or C-terminus of the sequence of SEQ ID NO: 1" (pg 8, lines 3-8). However, the specification of the instant application does not teach any fragments, variants, or derivatives of

an isolated BAFF-R polypeptide of SEQ ID NO: 1. The specification also does not teach any antibody that binds to fragments, variants, or derivatives of an isolated BAFF-R polypeptide of SEQ ID NO: 1. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding

site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, structurally similar proteins may have different functions and one skilled in the art cannot rely upon structural similarity alone to determine functionality. For example, the undisclosed polypeptide variants that are 80% or 90% similar to the amino acid sequence of SEQ ID NO: 1 may have different conformations and/or functions as compared to the disclosed polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The altered conformations and/or functions of the fragments and variants of BAFF-R may prevent the antibodies of the instant claims from binding. Daniel et al. (Virology 202: 540-549, 1994) also discloses that primary amino acid sequences do not predict antigenic determinants and therefore, changing the amino acid sequence of a polypeptide may also affect antigenicity (pg 540, 547).

Due to the large quantity of experimentation necessary to (1) inhibit B cell growth or immunoglobulin production or treat any autoimmune disease, renal disorder, B-cell lympho-proliferate disorder, hypertension, or inflammation by administration of an anti-BAFF-R antibody, (2) treat all possible autoimmune diseases, renal disorders, and B-cell lympho-proliferate disorders, and (3) generate all possible BAFF-R derivatives and anti-BAFF-R antibodies; the lack of direction/guidance presented in the specification regarding the same; the

absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of the effects of an anti-BAFF-R antibody *in vivo* (see discussion) and the unpredictability of the effects of protein alterations on antibody binding, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 1, 4-7, 11-12, 17-18, are 22-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of inhibiting B-cell growth, or immunoglobulin production, or both comprising the step of administering a therapeutically effective amount of an anti-BAFF-R antibody. The claims recite a method of treatment of an autoimmune disease, a method of treating hypertension, a method of treating renal disorders, a method of treating B-cell lympho-proliferate disorders, and a method of inhibiting inflammation comprising the step of administering an anti-BAFF-R antibody. The claims recite that the anti-BAFF-R antibody binds to a BAFF-R polypeptide. The claims recite that the anti-BAFF-R antibody is monoclonal, recombinantly produced, humanized, and chimeric.

The specification of the instant application teaches that " 'BAFF-R variant' means an active BAFF-R as defined below having at least about 80% amino acid sequence identity with the BAFF-R having the deduced amino acid sequence shown in SEQ ID NO: 1 for a full-length

native sequence BAFF-R or with a BAFF-R ECD sequence. Such BAFF-R variants include, for instance, BAFF-R polypeptides wherein one or more amino acid residues are added, or deleted, at the end or C-terminus of the sequence of SEQ ID NO: 1" (pg 8, lines 3-8).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in claim 11 only is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The specification teaches a BAFF-R polypeptide (SEQ ID NO: 1). However, the description of one polypeptide species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments and with at least 80% or 90% sequence identity to the BAFF-R polypeptide consisting of SEQ ID NO: 1 nor the antibodies that bind these fragments and variants.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides or the antibodies that bind these polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated antibody that binds to a protein consisting of the amino acid sequence of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 23-28 recite the limitation "anti-BAFF antibody". There is insufficient antecedent basis for this limitation in the claim. (Please note that this issue could be overcome by amending the claims to recite, for example, "anti-BAFF-R antibody".)

Priority

Applicant's claim for priority under 35 U.S.C. 120 and 119(e) is acknowledged. The polypeptide of SEQ ID NO: 1 and antibodies that bind the polypeptide of the instant application are fully disclosed in the prior applications of 60/149,378 (8/17/1999), 60/181,684 (2/11/2000), 60/183,536 (2/18/2000), and PCT/US00/22507 (8/16/2000). However, the applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. § 112, first paragraph for claims 1, 4-7, 11-12, 17-18, are 22-28 of this application. Therefore, claims 1, 4-7, 11-12, 17-18, are 22-28 are accorded the instant filing date of February 15, 2002 for the purposes of applying the prior art below.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 4,-7, 11-12, 17-18, 22-25, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Gross et al. (WO/200040716, published July 13, 2000).

Gross et al. teach a human BR43x2 polypeptide (SEQ ID NO: 8) that is 100% identical to the BAFF-R polypeptide of SEQ ID NO: 1 of the instant application (see sequence alignment attached to the instant Office Action as Appendix A). Gross et al. teaches that an isolated antibody that specifically binds to the isolated BR43x2 polypeptide of SEQ ID NO: 8 may be administered to a mammal (pg 2, lines 15-35). Gross et al. disclose that the anti-BR43x2 antibodies are polyclonal or monoclonal or humanized (pg 3, lines 29-33; pg 65, line 29 through pg 67). Gross et al. teach that the antibody is a $F(ab')_2$ fragment (pg 68, lines 6-9). Gross et al. teach that an anti-BR43x2 antibody can be obtained recombinantly or isolated from a natural source (pg 64, lines 23-28). It is noted that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

12. Claims 1, 4-7, 11-12, 17-18, and 22-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Shu et al. (U.S. Patent 6,475,987; issued November 5, 2000 with the benefit of provisional application 60/201,012 (May 1, 2000)).

Shu et al. teach a TALL-1 polypeptide (SEQ ID NO: 11) that is 100% identical to the BAFF-R polypeptide of SEQ ID NO: 1 of the instant application (see sequence alignment attached to the instant Office Action as Appendix B). Shu et al. teaches an isolated antibody that specifically binds to the isolated TALL-1 protein (col 3, lines 49-52; col 41, lines 40-50). Shu et al. disclose that an antibody composition may be delivered to a patient by any suitable method to reduce activity of the TALL-1 protein (col 28, lines 43-67; col 31, lines 17-61; col 33, lines 10-50). Shu et al. teach that the TALL-1 antibodies can be administered to any member of the vertebrate class, Mammalia, including humans (col 30, lines 8-31). Additionally, Shu et al. disclose that the anti-TALL-1 antibodies are polyclonal or monoclonal or functional equivalents, such as antibody fragments (col 22, lines 21-23). Shu et al. teach that the anti-TALL-1 antibodies may be single chain antibodies or chimeric antibodies, including bi-specific antibodies that can bind more than one epitope (col 22, lines 24-26). Shu et al. teach that the anti-TALL-1 antibodies may be produced recombinantly (col 22, lines 29-41). It is noted that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gross et al. (WO/200040716, published July 13, 2000) as applied to claims 1, 4,-7, 11-12, 17-18, 22-25, and 27-28 above, and further in view of Colcher et al. (Q J Nucl Med 43: 132-139, 1999).

The teachings of Gross et al. are set forth above.

Gross et al. does not teach an anti-BAFF antibody that is chimeric or that comprises human constant domains.

Colcher et al. disclose that antibody molecules can be engineered to modify functional domains such as antigen-binding sites and/or effector functions. Colcher et al. teach that researchers have used genetic engineering to create chimeric antibodies by joining the variable regions of mouse antibody to the constant regions of human immunoglobulin (pg 133, col 1, 3rd full paragraph). Colcher et al. also teach that human IgG1 or IgG3 constant regions would be the regions of choice for chimeric antibodies intended for use in antigen-dependent cytotoxicity and complement-dependent cytotoxicity (pg 133, col 2, first full paragraph). Colcher et al. disclose

that if the antibody is required for specific binding, IgG2 or IgG4 constant regions would be appropriate (pg 133, col 2, first full paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering an anti-BAFF-R antibody as taught by Gross et al. by utilizing a chimeric antibody (a chimeric anti-BAFF-R antibody) as taught by Colcher et al. The person of ordinary skill in the art would have been motivated to make that modification because chimeric antibodies reduce immunogenicity of administered immunoglobulin and select for desired subclass-associated Fc-mediated functions. The person of ordinary skill in the art reasonably would have expected success because a number of mouse/human chimeric antibodies were already being generated and utilized in clinical applications at the time the invention was made (for example, mouse/human chimeric antibodies against tumor-associated antigens). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

15. Claims 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shu et al. (U.S. Patent 6,475,987; issued November 5, 2000 with the benefit of provisional application 60/201,012 (May 1, 2000)) as applied to claims 1, 4-7, 11-12, 17-18, and 22-27 above, and further in view of Colcher et al. (Q J Nucl Med 43: 132-139, 1999).

The teachings of Shu et al. are set forth above.

Shu et al. does not teach an anti-BAFF antibody that is a $F(ab')_2$ fragment.

Colcher et al. disclose $F(ab')_2$ fragments prepared by pepsin digestion of an anti-CEA mouse-human chimeric monoclonal antibody of three different human IgG subclasses, IgG1, IgG2, and IgG4 (pg 134, col 1, lines 1-12).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering an anti-BAFF-R antibody as taught by Gross et al. by utilizing a $F(ab')_2$ fragment of anti-BAFF-R antibody as taught by Colcher et al. The person of ordinary skill in the art would have been motivated to make that modification because small size IgG fragments (Fab's) show fast clearance from serum and tissues and more effective tissue penetration than intact antibodies (Colcher et al. pg 135, bottom of col 1). The person of ordinary skill in the art reasonably would have expected success because $F(ab')_2$ fragments from antibodies were already being generated and utilized in clinical applications at the time the invention was made (for example, $F(ab')_2$ fragments from mouse/human chimeric antibodies against tumor-associated antigens). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure: (Other terms for BAFF include BlyS, neutrokine-alpha, TALL-1, THANK, and zTNF4)

Do et al. J Exp Med 192(7): 953-964, 2000. (apoptosis and Blys)

MacKay et al. J Exp Med. 190(11):1697-1710, 1999. (Mice transgenic for BAFF)

Moore et al. Science. 285(5425):260-263, 1999. (administration of Blys to mice)

Rennert et al. J Exp Med. 192(11):1677-1684, 2000. (APRIL)

Thompson et al. Science. 293(5537):2108-2111, 2001. (identification of BAFF-R)

Wu et al. J Biol Chem. 275(45):35478-35485, 2000. (TACI is receptor for BlyS and APRIL)

Yan et al. Nat Immunol. 1(1):37-41, 2000. (identification of a Blys receptor, TACI)

Yu et al. Nat Immunol. 1(3):252-256, 2000. (receptors for APRIL and TALL-1)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0883.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
30 March 2005

Bridget E. Bunner

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Db        181 ISAR 184

RESULT 2
AAY94001
ID   AAY94001 standard; protein; 184 AA.
XX
AC   AAY94001;
XX
DT   20-OCT-2000  (first entry)
XX
DE   A human BCMA protein, a B cell protein related to TACI.
XX
KW   Human; BR43x2; TACI receptor; extracellular domain; BCMA; B cell protein;
KW   transmembrane activator and CAML-interactor; tumour necrosis factor; TNF;
KW   ztnf4 activity; antibody production; autoimmune disease; amyloidosis;
KW   systemic lupus erythematosus; myasthenia gravis; multiple sclerosis;
KW   rheumatoid arthritis; asthma; bronchitis; emphysema; pyelonephritis;
KW   end stage renal failure; glomerulonephritis; vasculitis; nephritis;
KW   renal neoplasm; multiple myeloma; lymphoma; light chain neuropathy;
KW   immune response; immunosuppression; graft rejection; joint pain;
KW   graft versus host disease; inflammation; swelling; anaemia; septic shock;
KW   insulin dependent diabetes mellitus; Crohn's disease; hypertension;
KW   renal artery stenosis; occlusion; cholesterol; renal emboli.
XX
OS   Homo sapiens.
XX
PN   WO200040716-A2.
XX
PD   13-JUL-2000.
XX
PF   07-JAN-2000; 2000WO-US000396.
XX
PR   07-JAN-1999;   99US-00226533.
XX
PA   (ZYMO ) ZYMOGENETICS INC.
XX
PI   Gross JA,  Xu W,  Madden K,  Yee DP;
XX
DR   WPI; 2000-452538/39.
DR   N-PSDB; AAA58559.
XX
PT   Inhibiting ztnf4 activity in a mammal, to treat autoimmune diseases,
PT   renal disease, graft versus host disease, and inflammation, comprises
PT   administering a BR43x2, TACI or BCMA extracellular domain polypeptide.
XX
PS   Disclosure; Page 152; 175pp; English.
XX
CC   The present sequence represents a human BCMA protein, a B cell protein
CC   related to transmembrane activator and CAML-interactor (TACI) receptor.
CC   TACI is a tumour necrosis factor (TNF) receptor. The extracellular
CC   domains of BR43x2 (an isoform of TACI), TACI or BCMA (a related B cell
CC   protein) receptor contain a cysteine rich domain, and are used for
CC   inhibiting ztnf4 activity. Ztnf4 is a TNF ligand. They may also be used
CC   for inhibiting BR43x2, TACI or BCMA receptor-ligand engagement associated
CC   with activated or resting B lymphocytes, effector T-cells, or with
CC   antibody production. The antibody production is associated with an
CC   autoimmune disease selected from systemic lupus erythematosus, myasthenia
CC   gravis, multiple sclerosis and rheumatoid arthritis. The ztnf4 activity
CC   and BR43x2, TACI or BCMA receptor-ligand engagement is associated with
CC   asthma, bronchitis, emphysema, end stage renal failure,
CC   glomerulonephritis, vasculitis, nephritis, pyelonephritis, renal
CC   neoplasms, multiple myelomas, lymphomas, light chain neuropathy,
CC   amyloidosis, moderating immune response, immunosuppression, graft
CC   rejection, graft versus host disease, inflammation, insulin dependent
CC   diabetes mellitus, Crohn's disease, joint pain, swelling, anaemia, or
CC   septic shock. BR43x2, TACI, and BCMA polypeptides, fusions, antibodies,
CC   agonists or antagonists can be used to treat hypertension, renal artery
CC   stenosis, or occlusion, and cholesterol or renal emboli
XX
SQ   Sequence 184 AA;

  Query Match           100.0%;  Score 964;  DB 3;  Length 184;
  Best Local Similarity  100.0%;  Pred. No. 1e-94;
  Matches  184;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MLQMAGQCSQNEYFDSLLHACIPCQLRCSSNTPPLTCQRYCNASVTNSVKGTNAILWTCL 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MLQMAGQCSQNEYFDSLLHACIPCQLRCSSNTPPLTCQRYCNASVTNSVKGTNAILWTCL 60

Qy         61 GLSLIISLAVFVLMFLLRKISSEPLKDEFKNTGSGLLGMANIDLEKSRTGDEIILPRGLE 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GLSLIISLAVFVLMFLLRKISSEPLKDEFKNTGSGLLGMANIDLEKSRTGDEIILPRGLE 120

Qy        121 YTVEECTCEDCIKSKPKVDSDHCFPLPAMEEGATILVTTKTNDYCKSLPAALSATEIEKS 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 YTVEECTCEDCIKSKPKVDSDHCFPLPAMEEGATILVTTKTNDYCKSLPAALSATEIEKS 180

Qy        181 ISAR 184
              ||||
Db        181 ISAR 184
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Appendix B

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RESULT 1
US-09-565-423-11
; Sequence 11, Application US/09565423
; Patent No. 6475987
; GENERAL INFORMATION:
;  APPLICANT:  Shu, Hong-Bing
;  TITLE OF INVENTION:  TALL-1 NUCLEIC ACID MOLECULES, PROTEINS, RECEPTORS AND
;  TITLE OF INVENTION:  METHODS OF USE THEREOF
;  FILE REFERENCE:  2879-72
;  CURRENT APPLICATION NUMBER: US/09/565,423
;  CURRENT FILING DATE:  2000-05-05
;  PRIOR APPLICATION NUMBER:  UNKNOWN
;  PRIOR FILING DATE:  2000-05-01
;  PRIOR APPLICATION NUMBER:  60/132,892
;  PRIOR FILING DATE:  1999-05-06
;  NUMBER OF SEQ ID NOS:  17
;  SOFTWARE:  PatentIn Ver. 2.1
; SEQ ID NO 11
;   LENGTH: 184
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-09-565-423-11

  Query Match           100.0%;  Score 964;  DB 4;  Length 184;
  Best Local Similarity  100.0%;  Pred. No. 1e-103;
  Matches  184;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MLQMAGQCSQNEYFDSLLHACIPCQLRCSSNTPPLTCQRYCNASVTNSVKGTNAILWTCL 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MLQMAGQCSQNEYFDSLLHACIPCQLRCSSNTPPLTCQRYCNASVTNSVKGTNAILWTCL 60

Qy         61 GLSLIISLAVFVLMFLLRKISSEPLKDEFKNTGSGLLGMANIDLEKSRTGDEIILPRGLE 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GLSLIISLAVFVLMFLLRKISSEPLKDEFKNTGSGLLGMANIDLEKSRTGDEIILPRGLE 120

Qy        121 YTVEECTCEDCIKSKPKVDSDHCFPLPAMEEGATILVTTKTNDYCKSLPAALSATEIEKS 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 YTVEECTCEDCIKSKPKVDSDHCFPLPAMEEGATILVTTKTNDYCKSLPAALSATEIEKS 180

Qy        181 ISAR 184
              ||||
Db        181 ISAR 184


RESULT 2
US-09-949-016-11115
; Sequence 11115, Application US/09949016
; Patent No. 6812339
; GENERAL INFORMATION:
;  APPLICANT: VENTER, J. Craig et al.
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